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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte STALEY A. BROD

Appeal 2008-2763
Application 08/844,731
Technology Center 1600

Decided: January 16, 2009

Before TONI R. SCHEINER, DEMETRA J. MILLS, and LORA M. GREEN, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 8, 9, 11, 16, 17, 19, and 20. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

The claims are directed to a method of decreasing the incidence of insulin-dependent diabetes. Claim 8 is representative of the claims on appeal, and reads as follows:

8. A method of decreasing the incidence of insulin-dependent diabetes mellitus in at-risk populations:

orally administering 10,000 to 30,000 units of IFN-α to individuals of said at-risk population; and

immediately swallowing to ingest said IFN-α, thereby decreasing the incidence of insulin-dependent diabetes mellitus in the at-risk populations.

The Examiner relies on the following references:

Cummins, Jr. (Cummins '985)	US 4,462,985	Jul. 31, 1984
Cummins, Jr. (Cummins '382)	US 5,019,382	May 28, 1991
Sobel	US 5,780,021	Jul. 14, 1998

We affirm.

ISSUE

The Examiner concludes that claims 8, 9, 11, 16, 17, 19, and 20 would have been obvious under 35 U.S.C. § 103(a) over the combination of Sobel, Cummins '382, and Cummins '985.

Appellant contends that the references as combined do not render obvious the claimed dosage of 10,000 to 30,000 units of IFN-α.

Thus, the issue on Appeal is: Has the Appellant established that the Examiner erred in concluding that the references as combined render obvious the claimed method wherein the dosage is 10,000 to 30,000 units of IFN-α?

FINDINGS OF FACT

FF1 According to the Specification, "the present invention relates to . . . methods of treating auto-immune diseases using type one interferons." (Spec. 1.)

FF2 The Specification notes that "[h]uman IFN-α is an immunoactive protein that can be orally administered at low doses in the treatment of viral disease in animals." (*Id.* at 3.)

FF3 "Insulin-dependent diabetes mellitus (IDDM) is a chronic disorder that results from autoimmune destruction of the insulin-producing pancreatic b cell." (*Id.* at 4.)

FF4 Thus, in one embodiment of the invention, "there is provided a method of decreasing the incidence of insulin-dependent diabetes mellitus in at-risk populations, comprising the step of orally administering IFN-α to individuals of said at-risk population." (*Id.* at 6.)

FF5 Figure 12 of the Specification "shows subjects with early relapsing-remitting multiple sclerosis ingesting IFN-α demonstrate decreased Con A-mediated proliferation." (*Id.* at 15.) "Subjects with relapsing-remitting multiple sclerosis were administered IFN for two weeks at each dose with at least two weeks washout without IFN between the first dosing cycle (10,000 units), the second dosing cycle (30,000 units) and the third dosing cycle (100,000 units[])." (*Id.*) Peripheral blood mononuclear cells (PMNC) were then analyzed for CD3, Con A, and ionomycin + PMA proliferation (*id.*)

FF6 According to the Specification, "[t]here was no change in proliferation at the 100,000 unit dose or with CD3-mediated or ionomycin/PMA activation." (*Id.* at 15-16.)

FF7 Figure 18 "shows that every other day ingestion (oral) mIFN-α from age nine weeks suppresses the incidence of diabetes mellitus in NOD mice." (*Id.* at 17.) The mice were fed with mock IFN or 10 units of IFN-α three times per week, and those fed IFN-α "demonstrated delayed onset of IDDM and decreased frequency of animals becoming diabetic compared to untreated . . . animals." (*Id.*)

FF8 Similar results were seen in animals fed 10 units every day (*id.* at 18, Figure 20) and every other day (*id*, Figure 21).

FF9 The Examiner rejects claims 8, 9, 11, 16, 17, 19, and 20 under 35 U.S.C. § 103(a) as being obvious over the combination of Sobel, Cummins '382, and Cummins '985.

FF10 Sobel is cited for teaching a method of treating or preventing an auto-immune disease, such as IDDM, by administering IFN-α (Ans. 3 (citing Sobel cols. 1-2)). The Examiner also finds that such a method would inherently reduce blood glucose (Ans. 3).

FF11 The Examiner finds that Sobel teaches that "the amount of single subtype of α-IFN or β-IFN, hybrids, analogs, or mixtures thereof administered per dose either prior to or after the onset of disease is about $1x10^5$ units to about $75x10^6$ units with administration being given from once per day to about once per week." (*Id.* (quoting Sobel col. 4, ll. 10-16).) The Examiner finds moreover that Sobel teaches that the amount of α-IFN that may be administered may be $1x10^5$ units or less, such as $5x10^4$ units or less (Ans. 3 (citing Sobel col. 4, ll. 15-16).)

FF12 Figure 2 of Sobel "illustrates the effect of α-IFN (at 100,000 units/dose) treatment on the development of diabetes mellitus in DP-BB rats." (Sobel col. 2, ll. 1-3.)

FF13 According to the patent, the figure "shows that doses of α-IFN lower than 400,000 units may be used to reduce the incidence of diabetes mellitus. For example, a dose of as low as about 100,000 units may be used effectively." (*Id.* at col. 10, ll. 39-42.)

FF14 Sobel also teaches that

> the precise amount used will vary, depending upon the judgment of the attending physician, considering such factors as the age, weight and condition of the patient. While any mammal may be treated, such as dogs, cats, cows, horses, or poultry, it is particularly desirable that the mammal treated be human.

(*Id.* at col. 4, ll. 18-23.)

FF15 Finally, Sobel specifically teaches the formation of tablets, dragees, capsules and pills. (*Id.* at col. 11, l. 60-col. 12, l. 15.)

FF16 The Examiner notes that Sobel "does not teach the specific dosages recited in the claims and the alternate dosing." (Ans. 4.)

FF17 The Examiner cites Cummins '382 for teaching "the oral administration of about 0.1 to about 5 IU/lb per day of interferon." (Ans. 4 (citing Cummins '382 Abstract).)

FF18 The Examiner further finds that Cummins '382 teaches that 1 unit ≈ 0.1IU (Ans. 4 (citing Cummins '382 col. 3, ll. 54-55)); the treatment of autoimmune disorders (Ans. 4 (citing Cummins '382 col. 4, ll. 19-25)); and the use of a staggered regimen of doses, such as one to three days' treatment per week or month (Ans. 4 (citing Cummins '382 col. 5, ll. 51-55)).

FF19 The Examiner cites Cummins '985 for teaching "the oral administration in humans of 10 to 1,000 units of interferon per Kg body weight." (Ans. 4 (citing Cummins '985 col. 9, ll. 20-23).)

FF20 The Examiner further finds that Cummins '985 teaches that "dosages required for therapeutic effect are expected to vary widely depending on the mammal patient and condition treated, with from about 10 to about 1,000 units per Kg in unit dosage form being operative (column 9, lines 20-23)," which the Examiner finds translate to 870 to 87,000 units or 75 to 75,000 units for a human female patient and male patient, respectively (Ans. 4).

FF21 The Examiner concludes:

> It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made to practice the method of Sobel by modifying the doses as to taught by Cummins ('985) for the treatment of diabetes resulting in the claimed method because Cummins ('985) teaches that the dosages required for therapeutic effect are expected to vary widely dependent on the mammal patient and condition treated. See MPEP § 2144.05 [R-3] II for a discussion on optimization of ranges, specifically, *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382. One of ordinary skill in the art would have been motivated to use interferon in the doses recommended by Cummins ('985) to treat IDDM in the method of Sobel with the expectation of success because Cummins (U.S. Patent No: 5, 019, 382) teaches the treatment of autoimmune disorder, which includes IDDM and because Cummins ('985) teach that 10-100 unit per Kg is an operative range in humans. Therefore, the instant claims are *prima facie* obvious over Sobel (U.S. Patent No: 5,780,021) in view of Cummins (U.S. Patent No: 5, 019, 382) and Cummins (U.S. Patent No: 4, 462, 985).

(Ans. 4-5.)

PRINCIPLES OF LAW

"[D]uring examination proceedings, claims are given their broadest reasonable interpretation consistent with the specification." *In re Hyatt*, 211 F.3d 1367, 1372 (Fed. Cir. 2000).

> [T]he PTO applies to the verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification.

In re Morris, 127 F.3d 1048, 1054 (Fed. Cir. 1997).

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The Supreme Court has recently emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, __, 127 S. Ct. 1727, 1741 (2007).

Thus, as to motivation to combine, the Court rejected a rigid application of the teaching-suggestion-motivation test. The Court recognized that it is often necessary to look at the interrelated teachings of multiple references; the effects of demands of the marketplace; and the background knowledge possessed by a person of ordinary skill, "all in order to determine whether there was an apparent reason to combine the known

elements in the fashion claimed." *Id.* at 1740-41. Moreover, the "obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents." *Id.* at 1741. Finally, one "of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims." *Id.* at 1742. As also noted by the Court in *KSR*, "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton." *Id.* at 1742.

Moreover, determining the optimum values of result effective variables is ordinarily within the skill of the art. *See In re Boesch*, 617 F.2d 272, 276 (CCPA 1980); *see also In re Aller*, 220 F.2d 454, 456 (CCPA 1955) ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.").

Finally, the burden of demonstrating unexpected results rests on the party asserting them, and "it is not enough to show that results are obtained which differ from those obtained in the prior art: that difference must be shown to be an *unexpected* difference." *In re Klosak*, 455 F.2d 1077, 1080 (CCPA 1972). "Mere improvement in properties does not always suffice to show unexpected results." *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995). "[W]hen an applicant demonstrates *substantially* improved results, . . . and *states* that the results were *unexpected,* this should suffice to establish unexpected results *in the absence of* evidence to the contrary." *Id.*

When the prior art teaches a range, and the Applicant is claiming a narrower range than that taught by the prior art, an applicant can overcome a prima facie case of obviousness by demonstrating that the claimed range "is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range." *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (quoting *In re Geisler*, 116 F.3d 1465, 1469-70 (Fed. Cir. 1997). In addition, "the applicant's showing of unexpected results must be commensurate in scope with the claimed range." *Id.* Finally, "it is well settled that unexpected results must be established by factual evidence. 'Mere argument or conclusory statements in the specification does not suffice.'" *Geisler*, 116 F.3d at 1470 (quoting *In re DeBauwe*, 736 F.2d 699, 705 (Fed. Cir. 1994).

ANALYSIS

Appellant argues that the Examiner has failed to set forth a prima facie case of obviousness (App. Br. 3). Specifically, Appellant argues that Sobel does not teach or suggest the dose range of the instant claims (*id.*). According to Appellant, Sobel teaches administration of 1×10^5 to about 75×10^6 units, which, at a minimum, is three times higher than the dosage as required by the claims on appeal (*id.*). Appellant points to figures 1 and 2 Sobel, which show that 400,000 units of IFN was more effective at preventing IDDM than 100,000 units, and thus the reference does not teach or suggest using lower amount of IFN (*id.*).

Cummins '985, Appellant argues, is drawn to "the treatment of diseases that are not related to IDDM and thus . . . is not relevant to the

instant invention." (*Id.* at 4.) Thus, while Cummins '985 teaches a dosage range that comprises the instantly claimed dosage range, the reference does not teach controlling or suppressing an auto-immune disease such as IDDM, but is in fact drawn to the oral administration of IFN for enhancing immune response (*id.*).

Appellant asserts further that while Cummins '382 does concern the treatment of autoimmune diseases, the ranges are lower than those disclosed in Cummins '985 (*id.* at 5). Specifically, Appellant asserts, Cummins '382 "employs oral IFN dosages of about 0.01 to about 5 units per pound which is equivalent to about 19 to 963 units per individual for a male human." (*Id.*)

According to Appellant:

> These two references are by the same inventor and they teach different interferon dose ranges for use in treatment of different types of disease. When viewed together, these references would indicate to one of skill in the art that an interferon dose range effective to treat a particular disease will depend upon the disease type and thus the skilled artisan would not be motivated to combine the teachings of Sobel and Cummins '985 **especially in view of the teachings of Cummins '382.**

(*Id.*)

Appellant asserts further that "none of the references relied upon by the Examiner show actual working examples of **oral** administration of interferon for IDDM." (Reply Br. 6.)

Appellant's arguments are not found to be convincing. We first note that none of the claims (with the exception of claim 11), are drawn to any particular dosing schedule. Thus, the 10,000 to 30,000 units could be

administered four times daily (which would bring it to 120,000 units daily), three times daily, twice a day, once a day, etc.

Second, Sobel specifically discloses that the amount of α-IFN that may be administered may be $5x10^4$ (50,000) units or less. Cummins '382 and Cummins '985 teach lower amounts of interferon, with Cummins '382 being drawn to the treatment of autoimmune diseases (FF17-20). As noted by Appellant, Cummins '382 employs oral IFN dosages of about 0.01 to about 5 units per pound, which is equivalent to about 19 to 963 units per individual for a human male, and thus the prior art establishes a range of 19 units to 50,000 units, which encompasses the claimed range of 10,000 to 30,000 units. Both Sobel and Cummins '985 teach that it is understood that the amount administered would be within the level of skill in the art, depending on factors such as the condition of the patient, age and weight of the patient, as well as the mammal being treated (note that the claims 8, 9, 11, 16, and 17 are not limited to the treatment of humans) (FF14 and 20). Thus, it would be understood by the ordinary artisan that the range would differ depending on the condition of the patient, the patient's age, weight etc., and also whether the patient is a human or an at-risk mammal such as a dog or a cat, as would the frequency of dosing.

We have also considered Figure 2 of Sobel. But as the Sobel patent itself notes, the figure shows that doses of α-IFN lower than 400,000 may be used to reduce the incidence of diabetes mellitus. That teaching, along with Sobel's explicit teaching that doses as low as 50,000 units may be used, taken together with the teaching of the two Cummins patents, which teach administration of lower doses of α-IFN, would suggest to the ordinary

artisan that doses lower than 50,000 units, such as the doses claimed, could be effectively used to decrease the incidence of IDDM, delay the onset of IDDM, or reduce blood glucose levels.

Finally, even though the references have not specifically exemplified oral dosing of α-IFN in the treatment of IDDM, Cummins '382 does teach treatment of patients with other autoimmune diseases, such a rheumatoid arthritis and multiple sclerosis using oral administration of α-IFN (Cummins '382 col. 12, ll. 30-46). In addition, Sobel provides examples in which α-IFN administered intraperitoneally prevented the development of diabetes in diabetes prone rats (Sobel col. 9, l. 59-col. 10, l. 42), and also teaches that the α-IFN may be administered orally (*see, e.g.*, FF15). Thus, the prior art provides an expectation of success of preventing IDDM through the oral administration of α-IFN, and Appellant has provided no evidence to the contrary. Note that arguments of counsel cannot take the place of evidence in the record. *In re Scarbrough*, 500 F.2d 560, 566 (CCPA 1974).

Appellant stresses that "the present invention is directed to the discovery of a critical dosing range for ***oral*** administration of interferon for IDDM." (Reply Br. 6.) According to Appellant:

> We submit that this critical range is the only range found by the Appellant where interferon appears to be ***orally*** active to suppress immune cell proliferation in humans. In particular, when administered to a human with autoimmune disease 10,000 or 30,000 units of interferon resulted in reduced peripheral blood mononuclear cell (PBMC) proliferation, a measure of immune cell activation see figure 12 and page 16 line 24 through page 16 line 2 of the specification). High doses such as 100,000 units however lacked this effect. These studies therefore demonstrate that for oral administration a critical dose

> range (10,000 to 30,000 units/individual) is required therapeutic effect against immune cells.

(*Id.* at 7.)

First, we note that Appellant appears to be arguing unexpected results, which Appellant appears to have first presented in the Reply Brief, as we can find no reference to unexpected results in the Appeal Brief. Be that as it may, we find that the record on Appeal does not support a showing of unexpected results sufficient to overcome the prima facie case of obviousness.

Appellant relies on Figure 12 of the Specification in support of a critical dosing range and thus in support of unexpected results. (Reply Br. 7.) Figure 12, however, "shows subjects with early relapsing-remitting multiple sclerosis ingesting IFN-α demonstrate decreased Con A-mediated proliferation." (FF5.) Thus, Figure 12 is not drawn to decreasing the incidence of IDDM, delaying the onset of IDDM, or reducing blood glucose levels, as required by the claims. In addition, the treatment schedule was three times per week (Spec. 57), but the instant independent claims are not drawn to any specific dosing schedule. Finally, there is no evidence of record that *states* that the claimed range is *critical* to the claimed methods of decreasing the incidence of IDDM, delaying the onset of IDDM, or reducing blood glucose levels.

CONCLUSIONS OF LAW

We conclude that the Appellant has not established that the Examiner erred in concluding that the references as combined render obvious the

claimed method wherein the dosage is 10,000 to 30,000 units of IFN-α. We thus affirm the rejection of claims 8, 9, 11, 16, 17, 19, and 20 under 35 U.S.C. § 103(a) as being obvious over the combination of Sobel, Cummins '382, and Cummins '985.

TIME LIMITS

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

cdc

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